PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Prevalence of Charcot-Marie-Tooth Disease across the Lifespan: A Population-Based Epidemiological Study.
AUTHORS	Theadom, Alice; Roxburgh, Richard; MacAulay, Erin; O'Grady, Gina; Burns, J; Parmar, Priya; Jones, Kelly; Rodrigues, Miriam

VERSION 1 - REVIEW

REVIEWER	Carol Brayne University of Cambridge, Cambridge Institute of Public Health Cambridge UK
REVIEW RETURNED	07-Feb-2019

GENERAL COMMENTS	This is a well written classical descriptive neuroepidemiological study. It is carefully described, rigorous and intimate. I have only 2 minor comments: 2 d.p.s are rather unnecessary, 1 would suffice (spurious accuracy). Ethics needs to be corrected in more detail (identifiable and contact approaches) to help others who might want to conduct similar studies. Finally there are specific guidelines and neuroepidemiological studies (SIROND) for information.

REVIEWER	Davide Pareyson FondazioneIRCCS Istituto Neurologico Carlo Besta
REVIEW RETURNED	09-Mar-2019

GENERAL COMMENTS	This is a population-based study aimed at assessing the age-standardised prevalence of CMT in the Auckland region in New Zealand. The overall population is slightly less than 1,500,000 individuals and the authors could identify 236 affected adults and children, resulting in a prevalence of 15.7 per 100,000 for all CMT types (including CMT-related neuropathies, i.e., HNPP, HSAN and dHMN). Prevalence values were higher in the 50-64 year-old group and lower for girls under age 18. CMT1A prevalence was 6.9:100,000 and that of CMTX1 was surprisingly low, but only 42% of patients had received a genetic diagnosis. Medical records screening allowed the identification of the majority of cases, but community sources led to recruitment of further subjects (6.8%). The overall prevalence is higher than in the only previously conducted study assessing age-standardised prevalence (8.2 per 100,000 in Serbia) and is in keeping with other

	studies (average prevalence of 14.5 per 100,000 according to a recent systematic review, excluding the Norway study which reported a very high prevalence). The study is rigorous, well presented and important by increasing our knowledge on CMT epidemiology. It underlines the importance of using all available tools to identify CMT patients, and still the prevalence values are probably an underestimate. Indeed, it is likely that a proportion of CMT cases is not diagnosed, escapes ascertainment, or does not seek medical attention. With this respect, a recent study took advantage of a neonatal genetic screening program and found a prevalence of the PMP22 deletion associated with HNPP as high as 58.9 per 100,000 (Park et al. Frequency of hereditary neuropathy with liability to pressure palsies (HNPP) due to 17p11.2 deletion in a Korean newborn population. Orphanet J Rare Dis 2018;13:40)! It likely means that not all disease mutation carriers develop the disease at a significant extent and that prevalence estimates are influenced by the ascertainment tools employed. Such paper should be included in the reference list and commented. Two other recent papers (one just published) may be quoted, reporting higher CMT prevalence: Lousa et al. Genetic epidemiology, demographic, and clinical characteristics of Charcot-Marie-tooth disease in the island of Gran Canaria (Spain). J Peripher Nerv Syst. 2018 Dec 19. doi: 10.1111/jns.12299; Vaeth et al. Charcot-Marie-Tooth disease in Denmark: a nationwide register-based study of mortality, prevalence and incidence. BMJ Open. 2017 Nov 3;7(11):e018048.) The relatively low percentage of genetic diagnosis does not reduce the importance of the data, although it limits the analysis of subgroups. The low prevalence among girls and the higher rate of women among axonal CMT may be partly accounted for by CMTX1 cases among boys (earlier onset and more severe disease among males) and adult women (preserved nerve conduction values in CMTX1 females). Minor points. a) Introduction, page 5, first paragraph: The term “atrophy of neural tissue” may be misleading. I suggest: primarily characterised by demyelination of the nerves or degeneration of the axons. b) Is the prevalence of CMT1A reliable (40.9% of all cases, 6.9:100,000)? In other words, how many of the demyelinating cases performed genetic testing for the duplication?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

I have only 2 minor comments: 2 d.p.s are rather unnecessary, 1 would suffice (spurious accuracy).

d.p.s. have been reduced to 1 rather than two

Ethics needs to be corrected in more detail (identifiable and contact approaches) to help others who might want to conduct similar studies.

Further details on consent and contact approaches has been provided on pages 7 and 8

Finally there are specific guidelines and neuroepidemiological studies (SIROND) for information.

Thank you we have based the paper on these guidelines and ensured the required information is contained within the manuscript. However a checklist of these to complete and upload does not appear to be available.

Reviewer: 2

It underlines the importance of using all available tools to identify CMT patients, and still the prevalence values are probably an underestimate. Indeed, it is likely that a proportion of CMT cases is not diagnosed, escapes ascertainment, or does not seek medical attention. With this respect, a recent study took advantage of a neonatal genetic screening program and found a prevalence of the PMP22 deletion associated with HNPP as high as 58.9 per 100,000 (Park et al. Frequency of hereditary neuropathy with liability to pressure palsies (HNPP) due to 17p11.2 deletion in a Korean newborn population. Orphanet J Rare Dis 2018;13:40)! It likely means that not all disease mutation carriers develop the disease at a significant extent and that prevalence estimates are influenced by the ascertainment tools employed. Such paper should be included in the reference list and commented.

Thank you this paper has now been included in the discussion on page 17.

Two other recent papers (one just published) may be quoted, reporting higher CMT prevalence: Lousa et al. Genetic epidemiology, demographic, and clinical characteristics of Charcot-Marie-tooth disease in the island of Gran Canaria (Spain). J Peripher Nerv Syst. 2018 Dec 19. doi: 10.1111/jns.12299;

Vaeth et al. Charcot-Marie-Tooth disease in Denmark: a nationwide register-based study of mortality, prevalence and incidence. BMJ Open. 2017 Nov 3;7(11):e018048.)

Thank you these papers have now been cited as a comparison in the discussion on page 15

The relatively low percentage of genetic diagnosis does not reduce the importance of the data, although it limits the analysis of subgroups. The low prevalence among girls and the higher rate of women among axonal CMT may be partly accounted for by CMTX1 cases among boys (earlier onset and more severe disease among males) and adult women (preserved nerve conduction values in CMTX1 females).

Thank you for this suggestion which has been included in the discussion on page 16.

Minor points.

a) Introduction, page 5, first paragraph: The term “atrophy of neural tissue” may be misleading. I suggest: primarily characterised by demyelination of the nerves or degeneration of the axons.

Thank you for the suggestion this has been amended as suggested.

b) Is the prevalence of CMT1A reliable (40.9% of all cases, 6.9:100,000)? In other words, how many of the demyelinating cases performed genetic testing for the duplication?

73.2% of cases of CMT1a had received genetic confirmation of the duplication. This has now been stated on page 15 of the discussion.